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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,543	12/20/1999	SHUJI HINUMA	2472US0P	2478

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EXAMINER	
MITRA, RITA	
ART UNIT	**PAPER NUMBER**
1653	16

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/446,543	HINUMA ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2002* .

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,10,11,13,14 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10,11,13,14 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Applicants' amendment and response to office action dated April 9, 2002, filed on August 6, 2002 (paper #15) is acknowledged. Claims 5, 7-9, 12, 15 and 16 have been cancelled. Claims 1-4, 6, 10, 11, 13 and 14 have been amended. New claims 17-19 have been added. Therefore, claims 1-4, 6, 10, 11, 13, 14 and 17-19 are currently pending and are under examination.

Response to Remarks and Arguments

Withdrawal of Rejections

Objection to Specification

Objection to specification regarding continuing data and abstract has been withdrawn in view of Applicants' correction to specification.

Claims:

The rejection of claim 13 under **35 U.S.C. § 101** is withdrawn in view of Applicants' amendment to the claim.

The rejection of claims 1, 2, 3, 4, 6, 10, 11 and 14 under **35 U.S.C. § 112, second paragraph** is withdrawn in view of Applicants' amendment to the claims.

The rejection of claims 1-4 under **35 U.S.C. § 103(a)** as being unpatentable over Kask et al. taken with Zheng et al. and Lasa et al. is withdrawn in view of Applicants' amendment to claims 1-4.

Maintenance of Rejections

Rejections under 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in tbe art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 10, 11, 13, 14 and 17-19 remain/are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for an agent comprising a ligand polypeptide of full length sequence set forth in SEQ ID NO: 73; does not reasonably provide enablement for a substantial equivalent of that sequence or fragments generated from any position located on the sequence of SEQ ID NO: 73 or enablement of a sequence set forth in SEQ ID NO: 61. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants' reasons and arguments in response to the rejection are fully considered, however not found persuasive. The traversal is addressed along with the rejection as set forth below:

Claims 1-4, 6, 10, 11, 13, 14 and 17-19 encompass an agent for promoting prolactin secretion that comprises a ligand polypeptide, or a salt thereof, wherein the ligand polypeptide comprising an amino acid sequence of SEQ ID NO: 73, or fragments thereof, or a salt thereof (claim 1, 2), wherein said ligand polypeptide sequence comprises an amino acid sequence of SEQ ID NO: 74; an amino acid sequence of SEQ ID NO: 74 fused to the N-terminal of the amino acid sequence of SEQ ID NO: 73 (claim 2); an amino acid sequence of SEQ ID NO: 61 (claim 3); a method for promoting prolactin secretion in a mammal comprising administering an effective amount of the agent of claim 1 to said mammal (claim 4); a method for treating hypoovarianism in a mammal by administering an agent of claim 1(claim 6); a method for promoting lactation of a mammal by administering an agent of claim 1 (claim 10); a method for eliciting an aphrodisiac effect in a mammal by administering an agent of claim 1 (claim 11); a method for making a pharmaceutical for promoting prolactin secretion using the ligand polypeptide of claim 1 (claim 13); a method for promoting prolactin secretion in a mammal, which comprises administering to said mammal the ligand polypeptide (claim 14); a method for promoting lactation in a mammal, which comprises administering to said mammal the ligand polypeptide of claim 2 (claim 17); a method for treating hypoovarianism in a mammal by administering an agent of claim 2 (claim 18); a method for eliciting an aphrodisiac effect in a mammal by administering an agent of claim 2(claim 19).

Applicants' ground of traversal is the specification clearly provides the information for the structure and asserted function of the claimed invention, in particular on pages 20-22 or 29-30 (see page 10 of the remarks). The specification, however, only discloses (see page 4-5) without data to support the findings, which state that the ligand polypeptide of the agent is a polypeptide comprising an amino acid sequence represented by SEQ ID NO: 73 or a substantial equivalent thereto (page 4, lines 11-15). While defining "substantial equivalent" at page 19 specification indicates that it means the binding activity of the ligand and the receptor and physical characteristics are substantially same, and polypeptides containing the substitution, deletion or insertion would be considered to be substantially equivalent to polypeptides lacking the substitution deletion or insertion. There are no indicia that the present application enables the full scope in view of the amino acid sequences corresponding to a 'substantially equivalent' of the sequence as set forth in SEQ ID NO: 73 as discussed in the following stated rejection. The specification further indicates (see page 22) that the ligand polypeptide of the present invention can be changed or mutated by substitution, deletion, addition or modification to a polypeptide, which is stable against heat or proteases, or a polypeptide whose physiological function is activated. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed. Applicants' statement at page 10 is not persuasive because the description given at pages 20-22 or 29-30 are not specific, also no biological activities are described for the mutants and fragments that would be generated from SEQ ID NO: 73 or SEQ ID NO: 74.

The breadth of the claims is broad and encompasses an unspecified amount of variants regarding the ligand polypeptide of SEQ ID NO: 73, SEQ ID NO: 74 and SEQ ID NO: 61 as biological active variants, which are not specifically described or demonstrated in the specification.

Applicants have commented at page 11 in paragraph 2 that given the demonstrated structure, function and activity of the exemplar species of the protein of the claimed invention described in detail in the specification, one of ordinary skill in the art would find sufficient guidance, and direction to prepare the species of the claimed invention. However, Applicants' comments are not persuasive because the statement does not address the entire rejection as set

forth in previous office action. Moreover, amended claims do not remove the deficiency to overcome the scope rejection as discussed below:

Claims 1 and 2 are directed to an agent for promoting prolactin secretion that comprises a ligand polypeptide, wherein the ligand polypeptide comprising an amino acid sequence represented by SEQ ID NO: 73, or fragments thereof. The specification describes a ligand polypeptide for G protein-coupled receptor protein and shows the influence of this polypeptide on prolactin secretion (see Examples 46, 47, 49). None of the examples provide any indication that the ligand polypeptide fragments or mutants would influence the promotion of prolactin secretion thus part of claim 1 and 2 (mutants and fragments) is not enabled by the description. Furthermore no biological activities were attributed to the recited variants and the structural information was limited (see specification page 21, lines 22-36, page 22, lines1-6). There is no disclosure about the biological activities of the claimed variants. Identification of the ligand polypeptide is described in Example 21 of the specification and its function for promoting prolactin secretion were described in *in vivo* assay of Examples 46, 47, however specification fails to provide any description or demonstration of a variant of ligand polypeptide of SEQ ID NO: 73 or SEQ ID NO: 74 or SEQ ID NO: 61 sequence promoting prolactin secretion. For these reasons, it requires undue experimentation to make the claimed invention, especially where in claims 1, 2 and 3, substantial equivalents would have been included by the claims and for which the specification does not describe with particularity as to retention of function. Without any guidance or suggestions a skilled artisan would not be able to predict the structure of a variant that would demonstrate the same activity as the activity of the ligand polypeptide sequence of SEQ ID NO: 73 and SEQ ID NO: 61. Thus, for the reasons set forth above, undue experimentation is required to make and use the claimed fragments.

Claims 6, 10 and 11 are directed to the use of the agent of claim 1 for treating hypoovarianism (claim 6), for promoting lactation of a mammal (claim 10), and for eliciting an aphrodisiac effect (claim 11). However, there is no disclosure of the use of any variant for any treatment or for any induction/influence as claimed for the ligand polypeptide. For these reasons, it requires undue experimentation to make thc claimed invention.

Claim 13 is directed to a method for manufacture of a pharmaceutical for promoting prolactin secretion using the ligand polypeptide of claim 1. Specification at pages 39-41 describes the pharmaceutical composition comprising the ligand polypeptide, however specification fails to provide any use of the variants for manufacturing of a pharmaceuticals that promotes prolactin secretion.

Claim 14 is directed to a method for promoting prolactin secretion in a mammal, which comprises administering to said mammal the ligand polypeptide of claim 1. Specification at pages 67-69 provides a general description of the application of the ligand polypeptide and also describes an administration of the polypeptide (Example 49) to rats that increases prolactin secretion. However specification fails to provide description for the use of the variants of ligand polypeptides in the claimed method. For the reasons set forth above, undue experimentation is necessary to make and use the claimed fragments that retain the property of promoting prolactin secretion.

Claims 18, 17 and 19 are directed to the use of the agent of claim 2 for treating hypoovarianism (claim 18), for promoting lactation of a mammal (claim 17), and for eliciting an aphrodisiac effect (claim 19). However, there is no disclosure of the use of any variant for any treatment or for any induction/influence as claimed for the ligand polypeptide. For these reasons, it requires undue experimentation to make the claimed invention.

As discussed above, the specification provides only a generic description of how a variety of variants of ligand polypeptide can be generated (page 19-21), no specific guidance is provided on the generation of the fragments that demonstrate the biological activity of the ligand sequences of SEQ ID NO: 73 or SEQ ID NO: 74. There are no working examples of these variants in the specification. While the specification in Example 46 and 47 describes and demonstrates that the ligand polypeptide set forth in SEQ ID NO: 73 having prolactin secretion function, there is no disclosure about the biological activities of the claimed variants of ligand polypeptide. Since the specification fails to provide sufficient guidance on the structure and function of the various variants, it is necessary to have additional guidance on the identities of fragments to carry out further experimentation to assess their property of having prolactin secretion function.

The prior art has shown an agent as well as a ligand polypeptide for a G protein-coupled receptor protein for modulating prolactin secretion (see section below of 102(e) rejection), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structure and function for various amino acid sequences to be considered enabling for variants/fragments for ligand polypeptide. Furthermore, prior art demonstrates the enablement of a specific ligand polypeptide that couples with a specific G protein-coupled receptor to modulate pituitary function, prior art doesn't describe the enablement of any agent comprising any ligand polypeptide that binds with any G protein-coupled receptor protein to modulate the prolactin secretion as claimed in the instant application. Moreover, the prior art does not demonstrate enablement of any mutants or fragments of such a ligand polypeptide.

Applicants have submitted two references in support of their assertion. Hinuma et al. (Nature, 393, 272-276, 1998) and Kawamata et al. (Endocrine, 12, 215-221, 2000) references have been reviewed. However none of the articles describe any mutants/fragments that promote the prolactin secretion as claimed in the instant invention. Therefore, these references do not overcome the scope rejection.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because in summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable for the various modified forms, it is necessary to have additional guidance and to carry out further experimentation to assess the property of the variants. Therefore, due to large quantity of experimentation necessary to determine an activity or property of the disclosed ligand polypeptide and the fragments thereof, such that it can be determined how to use the claimed ligand polypeptide, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the specification fails to teach the skilled artisan how to make and use the claimed invention.

New ground of rejection

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Hinuma et al. (US Patent 6, 228,984, Issued May 8, 2001; 102(e) date: February 6, 1997). Hinuma et al. teach a novel ligand polypeptide for the G protein-coupled receptor protein, having an amino acid sequence set forth in SEQ ID NO: 73 or its substantial equivalent thereto, or its amide or ester or salt thereof (US '984 technical field col. 1; col. 2 lines 36-39 and claim 1), wherein the pharmaceutical composition containing the said polypeptide is a pituitary function modulator ('984, col. 3, lines 15-17). Hinuma's polypeptide has 96.3% sequence identity to SEQ ID NO: 73 (see alignment result, Database: A_Geneseq_032802, AC NO: AAW31394) (claim 1, 2) and has 91.5% sequence identity to SEQ ID NO: 74 (see alignment result, Database: A_Geneseq_032802, AC NO: AAW31384) (claim 2 (i)). Hinuma et al. also teach a polypeptide which comprises an amino acid sequence wherein the peptide of SEQ ID NO: 74 is added to the N-terminus of the polypeptide comprising the amino acid sequence of SEQ ID NO: 73 ('984 col. 4, lines 12-16), wherein the fused polypeptide has 94.2% sequence identity to SEQ ID NO: 74 fused to SEQ ID NO: 73 (see alignment result, Database: A_Geneseq_032802, AC NO: AAW31391) (claim 2 (ii)). Further Hinuma et al. teach a polypeptide fragment (see '984, col. 2, lines 40-47 and claim 2) that comprises an amino acid sequence having 100% sequence identity to SEQ ID NO: 61 (see alignment result, Database: A_Geneseq_032802, AC NO: AAW31391) (claim 3). Hinuma's polypeptide having SEQ ID NO: 73, SEQ ID NO: 74 and the fused products and fragments thereof; a fragment having SEQ ID NO: 61 are considered for the agent for promoting prolactin secretion which comprises an isolated ligand polypeptide having amino acid

sequence of SEQ ID NO: 73, SEQ ID NO: 74 and the fused products and fragments thereof, a fragment having SEQ ID NO: 61 (claims 1-3). Therefore, claims 1-3 of the instant application are anticipated by Hinuma et al. because items (i) through (iv) are variable as to the exact sequence.

Conclusion

No claim is allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr.Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Rita Mitra, Ph.D.
April 6, 2002